

EXHIBIT A

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A NOVEL HERBAL COMPOSITION FOR THE TREATMENT OF GASTRIC ULCER

Field of the Invention

5 The present invention relates to a novel synergistic herbal composition for the treatment of gastric ulcer. The present invention also relates to a method for the preparation of the composition. The present invention further relates to a process for the treatment of gastric ulcer using the composition.

Background and prior art to the Invention

10 Various theories have been proposed with respect to a cause of ulcer in human. In particular, it has been elucidated that stress, taking of non-steroidal anti-inflammatory drugs for curing rheumatic diseases, and the like are closely related to ulcer formation, mainly due to relatively excess gastric or duodenal acid secretion. Accordingly it is important to suppress the acid secretion in order to prevent ulcer formation and to cure it.

15 On the other hand it has been considered that *Helicobacter pylori*, which is a rod normally existing in stomach, generates ammonia due to its strong urease activity, thereby inducing ulcer. Since, it persistently lives within mucus and mucosa, it becomes the greatest cause for recurrence of ulcer. Accordingly, it has been considered that the recurrence of ulcer can be prevented, if this bacterium is sterilized.

20 References may be made to K.M. Nadkarni in Indian Materia Medica (1976) Vol. 1, p 74-76, 155, published by Popular Prakashan Pvt. Ltd., Mumbai; K.R. Kirtikar in Indian Medicinal Plants (1975) Vol. 4, p 2505 published by Bishen Singh Mahendrapal Singh, Dehradun and P.K. Warrier in Indian Medicinal Plants- A compendium of 500 species (1994-1996) Vol. 1, p 103 for the various medicinal properties of *Aloe barbadensis*.

25 References may be made to K.M. Nadkarni in Indian Materia Medica (1976) Vol. 1, p 155 published by Popular Prakashan Pvt. Ltd., Mumbai; K.R. Kirtikar in Indian Medicinal Plants (1975) Vol. 4, p 2249 published by Bishen Singh Mahendrapal Singh, Dehradun; P.K. Warrier in Indian Medicinal Plants- A compendium of 500 species (1994-1996) Vol. 1, p 218, and K. Narayana Iyer and M. Kolammal in Pharmacognosy of Ayurvedic Drugs

30 (1963) Series 1, No. 6, p. 48 published by Department of Pharmacognosy, University of Kerala, Trivandrum for the various medicinal properties of *Asparagus racemosus*. References may be made to K.M. Nadkarni in Indian Materia Medica (1976) Vol. 1, p 582 published by Popular Prakashan Pvt. Ltd., Mumbai; K.R. Kirtikar in Indian Medicinal Plants (1975) Vol. 1, p. 728 published by Bishen Singh Mahendrapal Singh, Dehradun;

35 P.K. Warrier in Indian Medicinal Plants- A compendium of 500 species (1994-

1996) Vol. 3, p 84, 86-87; The Wealth of India (1950-1980) Vol. 4, p. 152-153, published by Council of Scientific and Industrial Research; S.S. Handa in Indian Herbal Pharmacopeia (1998), p. 96, published by Regional Research Laboratory, Jammu and IDMA, Mumbai; Y.K. Sarin in Illustrated lanual of herbal drugs used in Ayurveda (1996),
 5 p. 116, and The Ayurvedic Pharmacopoeia of India, Vol. 1, p. 128, published by Ministry of Health and Family Welfare, India for the various medicinal properties of *Glycyrrhiza glabra*.

References may be made to K.M. Nadkarni in Indian Materia Medica (1976) Vol. 1, p. 1127-28, published by Popular Prakashan Pvt. Ltd., Mumbai; K.R. Kirtikar in Indian
 10 Medicinal Plants (1975) Vol. 3, p 1858-89 published by Bishen Singh Mahendrapal Singh, Dehradun; P.K. Warrier in Indian Medicinal Plants- A compendium of 500 species (1994-1996) Vol. 5, p 104, and The Wealth of India (1950-1980) Vol. 9, p. 290, published by Council of Scientific and Industrial Research for the various medicinal properties of *Sesamum indicum*.

15 References may be made to K.M. Nadkarni in Indian Materia Medica (1976) Vol. 1, p 531, published by Popular Prakashan Pvt. Ltd., Mumbai; P.K. Warrier in Indian Medicinal Plants- A compendium of 500 species (1994-1996) Vol. 3, p. 11-12, and K. Narayana Iyer and M. Kolammal in Pharmacognosy of Ayurvedic Drugs (1963) Series 1, No. 6, p. 1, published by Department of Pharmacognosy, University of Kerala, Trivandrum for the
 20 various medicinal properties of *Evolvulus alsinoides*.

References may be made to K.M. Nadkarni in Indian Materia Medica (1976) Vol. 1, p822-825, published by Popular Prakashan Pvt. Ltd., Mumbai; K.R. Kirtikar in Indian Medicinal Plants (1975) Vol. 4, p. 2454, published by Bishen Singh Mahendrapal Singh, Dehradun, and P.K. Warrier in Indian Medicinal Plants- A compendium of 500 species (1994-1996)
 25 Vol. 4, p 78 for the various medicinal properties of *Musa sapientum*.

References may be made to K.M. Nadkarni in Indian Materia Medica (1976) Vol. 1, p 1028-1030, published by Popular Prakashan Pvt. Ltd., Mumbai; P.K. Warrier in Indian Medicinal Plants- A compendium of 500 species (1994-1996) Vol. 3, p. 299, published by orient Longman, Chennai; The Wealth of India (1950-1980) Vol. 10, p. 271, published by
 30 Council of Scientific and Industrial Research; Y.K. Sarin in Illustrated lanual of herbal drugs used in Ayurveda (1996), p. 202, and The Ayurvedic Pharmacopoeia of India, Vol. 1, p. 3, published by Ministry of Health and Family Welfare, India for the various medicinal properties of *Trachyspermum roxburghianum*.

References may be made to K.M. Nadkarni in Indian Materia Medica (1976) Vol. 1, p. 478, published by Popular Prakashan Pvt. Ltd., Mumbai; K.R. Kirtikar in Indian Medicinal Plants (1975) Vol. 2, p. 1479, published by Bishen Singh Mahendrapal Singh, Dehradun; P.K. Warrier in Indian Medicinal Plants- A compendium of 500 species (1994-1996) Vol. 2, p. 368, published by orient Longman, Chennai; The Wealth of India (1950-1980) Vol. 3, p. 167, published by Council of Scientific and Industrial Research; Y.K. Sarin in Illustrated lanual of herbal drugs used in Ayurveda (1996), p. 290, and The Ayurvedic Pharmacopoeia of India, Vol. 1, p. 124, published by Ministry of Health and Family Welfare, India for the various medicinal properties of *Embelia ribes*.

10 References may be made to K.M. Nadkarni in Indian Materia Medica (1976) Vol. 1, p. 381-82, published by Popular Prakashan Pvt. Ltd., Mumbai; K.R. Kirtikar in Indian Medicinal Plants (1975) Vol. 2, p. 1225, published by Bishen Singh Mahendrapal Singh, Dehradun; P.K. Warrier in Indian Medicinal Plants- A compendium of 500 species (1994-1996) Vol. 2, p. 184, published by orient Longman, Chennai, and The Wealth of India (1950-1980) Vol. 3, p. 349, published by Council of Scientific and Industrial Research for the various medicinal properties of *Coriandrum sativum*.

Reference may be made to P.K. Warrier in Indian Medicinal Plants- A compendium of 500 species (1994-1996) Vol. 2, p. 277, published by orient Longman for the various medicinal properties of *Cyclea peltata*.

20 References may be made to K.M. Nadkarni in Indian Materia Medica (1976) Vol. 1, p. 537, published by Popular Prakashan Pvt. Ltd., Mumbai; K.R. Kirtikar in Indian Medicinal Plants (1975) Vol. 2, p. 1217, published by Bishen Singh Mahendrapal Singh, Dehradun; P.K. Warrier in Indian Medicinal Plants- A compendium of 500 species (1994-1996) Vol. 3, p. 13, published by orient Longman, Chennai; Y.K. Sarin in Illustrated lanual of herbal drugs used in Ayurveda (1996), p. 332, and The Ayurvedic Pharmacopoeia of India, p. 50, published by Ministry of Health and Family Welfare, India for the various medicinal properties of *Ferula usafotida*.

The composition of the present invention should not be treated as an obvious one as none of the citations are able to provide all the advantages of the present invention.

30 Objects of the Invention

The main object of the present invention is to provide a novel synergistic hérbal composition for the treatment of gastric ulcer

Yet another object of the present invention is to provide a process for the preparation of the composition.

Still another object of the present invention is to provide a method for the treatment of gastric ulcer using the composition.

5 **Summary of the Invention**

The present invention provides a novel synergistic herbal composition for the treatment of gastric ulcer. Also, the present invention provides a process for the preparation of the composition. The present invention further provides a method for the treatment of gastric ulcer using said composition.

10 **Detailed Description of the present Invention**

In accordance with the first embodiment of the present invention, there is provided a synergistic herbal composition for the treatment of gastric ulcer, said composition essentially comprising of powdered plant parts of *Asparagus racemosus*, *Glycyrrhiza glabra*, *Sesamum indicum*, *Musa sapientum* and *Trachyspermum roxburghianum* and 15 optionally, powdered plant parts of *Cyclea peltata*, *Embelia ribes*, *Coriandrum sativum*, *Ferula asafoetida*, *Aloe barbadensis* and *Evolvulus alsinoides* along with one or more pharmaceutically acceptable additives/carriers.

In an embodiment of the present invention, the composition comprises powdered plant parts of *Asparagus racemosus*, *Glycyrrhiza glabra*, *Sesamum indicum*, *Musa sapientum* 20 and *Trachyspermum roxburghianum* in equal proportions, optionally along with one or more pharmaceutically acceptable additives/carriers. This composition is hereafter referred to as HF3.

In another embodiment of the present invention, the composition comprises powdered plant parts of *Asparagus racemosus*, *Glycyrrhiza glabra*, *Sesamum indicum*, *Musa sapientum*, *Trachyspermum roxburghianum*, *Evolvulus alsinoides* and *Ferula asafoetida* 25 in equal proportions, optionally along with one or more pharmaceutically acceptable additives/carriers. This composition is hereafter referred to as HF4.

In yet another embodiment of the present invention, the composition comprises powdered plant parts of *Asparagus racemosus*, *Glycyrrhiza glabra*, *Sesamum indicum*, *Musa sapientum*, *Trachyspermum roxburghianum*, *Evolvulus alsinodes*, *Ferula asafoetida*, *Coriandrum sativum*, *Cyclea peltata* and *Aloe barbadensis* in equal proportions, optionally 30 along with one or more pharmaceutically acceptable additives/carriers. This composition is hereafter referred to as HF5.

In still another embodiment of the present invention, the composition comprises 5-13 wt. % of powdered plant parts of *Asparagus racemosus*, 5-12 wt. % of powdered plant parts of *Glycyrrhiza glabra*, 8-14 wt. % of powdered plant parts of *Sesamum indicum*, 7-14 wt. % of powdered plant parts of *Musa sapientum*, 4-12 wt. % of powdered plant parts of 5 *Trachyspermum roxburghianum*, 6-12 wt. % of powdered plant parts of *Aloe barbadensis*, 5-12 wt. % of powdered plant parts of *Evolvulus alsinoides*, 6-13 wt. % of powdered plant parts of *Cyclea peltata*, 9-14 wt. % of powdered plant parts of *Embelia ribes*, 7-14 wt. % of powdered plant parts of *Coriandrum sativum* and 8-13 wt. % of plant parts of *Ferula asafoetida*, optionally along with one or more pharmaceutically acceptable 10 additives/carriers. This composition is hereafter referred to as HF2.

In one more embodiment of the present invention, the plant part of *Trachyspermum roxburghianum*, *Embelia ribes* and *Coriandrum sativum* is fruit.

In one another embodiment of the present invention, the plant part of *Cyclea peltata* and *Glycyrrhiza glabra* is root.

15 In a further embodiment of the present invention, the plant part of *Aloe barbadensis* is elio. In a furthermore embodiment of the present invention, the plant part of *Asparagus racemosus* is tuber.

In an embodiment of the present invention, the plant part of *Sesamum indicum* is seed.

20 In another embodiment of the present invention, the plant part of *Musa sapientum* is unripe fruit.

In yet another embodiment of the present invention, the plant part of *Ferula asafoetida* is resin.

25 In accordance with the another embodiment of the present invention, there is provided a synergistic herbal composition for the treatment of gastric ulcer, said composition comprising equal proportions of 10 powdered plant parts selected from the group comprising of powdered plant parts of *Asparagus racemosus*, *Glycyrrhiza glabra*, *Sesamum indicum*, *Musa sapientum*, *Trachyspermum roxburghianum*, *Cyclea peltata*, *Embelia ribes*, *Coriandrum sativum*, *Ferula asafoetida*, *Aloe barbadensis* and *Evolvulus alsinoides*, optionally along with one or more pharmaceutically acceptable 30 additives/carriers.

In an embodiment of the present invention, said composition comprises equal proportions of powdered plant parts of *Asparagus racemosus*, *Glycyrrhiza glabra*, *Sesamum indicum*, *Musa sapientum*, *Trachyspermum roxburghianum*, *Cyclea peltata*, *Embelia ribes*,

Coriandrum sativum, Ferula asafoetida and *Aloe barbadensis*, optionally along with one or more pharmaceutically acceptable additives/carriers.

In another embodiment of the present invention, said composition comprises equal proportions of powdered plant parts of *Asparagus racemosus, Glycyrrhiza glabra,*

5 *Sesamum indicum, Musa sapientum, Trachyspermum roxburghianum, Cyclea peltata, Embelia ribes, Coriandrum sativum, Ferula asafoetida* and *Evolvulus alsinoides*, optionally along with one or more pharmaceutically acceptable additives/carriers.

In yet another embodiment of the present invention, said composition comprises equal proportions of powdered plant parts of *Asparagus racemosus, Glycyrrhiza glabra,*

10 *Sesamum indicum, Musa sapientum, Trachyspermum roxburghianum, Cyclea peltata, Embelia ribes, Coriandrum sativum, Aloe barbadensis* and *Evolvulus alsinoides*, optionally along with one or more pharmaceutically acceptable additives/carriers.

In still another embodiment of the present invention, said composition comprises equal proportions of powdered plant parts of *Asparagus racemosus, Glycyrrhiza glabra,*

15 *Sesamum indicum, Musa sapientum, Trachyspermum roxburghianum, Cyclea peltata, Embelia ribes, Ferula asafoetida, Aloe barbadensis* and *Evolvulus alsinoides*, optionally along with one or more pharmaceutically acceptable additives/carriers.

In one more embodiment of the present invention, said composition comprises equal proportions of powdered plant parts of *Asparagus racemosus, Glycyrrhiza glabra,*

20 *Sesamum indicum, Musa sapientum, Trachyspermum roxburghianum, Cyclea peltata, Coriandrum sativum, Ferula asafoetida, Aloe barbadensis* and *Evolvulus alsinoides*, optionally along with one or more pharmaceutically acceptable additives/carriers.

In one another embodiment of the present invention, said composition comprises equal proportions of powdered plant parts of *Asparagus racemosus, Glycyrrhiza glabra,*

25 *Sesamum indicum, Musa sapientum, Trachyspermum roxburghianum, Embelia ribes, Coriandrum sativum, Ferula asafoetida, Aloe barbadensis* and *Evolvulus alsinoides*, optionally along with one or more pharmaceutically acceptable additives/carriers.

In a further embodiment of the present invention, said composition comprises equal proportions of powdered plant parts of *Asparagus racemosus, Glycyrrhiza glabra,*

30 *Sesamum indicum, Musa sapientum, Cyclea peltata, Embelia ribes, Coriandrum sativum, Ferula asafoetida, Aloe barbadensis* and *Evolvulus alsinoides*, optionally along with one or more pharmaceutically acceptable additives/carriers.

In a further more embodiment of the present invention, said composition comprises equal proportions of powdered plant parts of *Asparagus racemosus*, *Glycyrrhiza glabra*, *Sesamum indicum*, *Trachyspermum roxburghianum*, *Cyclea peltata*, *Embelia ribes*, *Coriandrum sativum*, *Ferula asafoetida*, *Aloe barbadensis* and *Evolvulus alsinoides*,

5 optionally along with one or more pharmaceutically acceptable additives/carriers.

In an embodiment of the present invention, said composition comprises equal proportions of powdered plant parts of *Asparagus racemosus*, *Glycyrrhiza glabra*, *Musa sapientum*, *Trachyspermum roxburghianum*, *Cyclea peltata*, *Embelia ribes*, *Coriandrum sativum*, *Ferula asafoetida*, *Aloe barbadensis* and *Evolvulus alsinoides*, optionally along with one

10 or more pharmaceutically acceptable additives/carriers.

In another embodiment of the present invention, said composition comprises equal proportions of powdered plant parts of *Asparagus racemosus*, *Sesamum indicum*, *Musa sapientum*, *Trachyspermum roxburghianum*, *Cyclea peltata*, *Embelia ribes*, *Coriandrum sativum*, *Ferula asafoetida*, *Aloe barbadensis* and *Evolvulus alsinoides*, optionally along

15 with one or more pharmaceutically acceptable additives/carriers.

In yet another embodiment of the present invention, said composition comprises equal proportions of powdered plant parts of *Glycyrrhiza glabra*, *Sesamum indicum*, *Musa sapientum*, *Trachyspermum roxburghianum*, *Cyclea peltata*, *Embelia ribes*, *Coriandrum sativum*, *Ferula asafoetida*, *Aloe barbadensis* and *Evolvulus alsinoides*, optionally along

20 with one or more pharmaceutically acceptable additives/carriers.

In accordance with the second embodiment of the present invention, there is provided a process for the preparation of the novel synergistic herbal composition for the treatment of gastric ulcer, said process comprising the steps of powdering plant parts essentially selected from *Asparagus racemosus*, *Glycyrrhiza glabra*, *Sesamum indicum*, *Musa sapientum* and *Trachyspermum roxburghianum* and optionally, selected from *Cyclea peltata*, *Embelia ribes*, *Coriandrum sativum* *Ferula asafoetida*, *Aloe barbadensis* and *Evolvulus alsinoides*, mixing the aforesaid powdered plant parts to obtain a mixture and optionally adding one or more pharmaceutically acceptable additives/carriers to the above mixture.

25 30 In an embodiment of the present invention, said process comprises the steps of powdering plant parts of *Asparagus racemosus*, *Glycyrrhiza glabra*, *Sesamum indicum*, *Musa sapientum* and *Trachyspermum roxburghianum*, mixing the aforesaid plant parts in equal

proportions to obtain a mixture and optionally adding one or more pharmaceutically acceptable additives/carriers to the above mixture.

In another embodiment of the present invention, said process comprises the steps of 5 powdering plant parts of *Asparagus racemosus*, *Glycyrrhiza glabra*, *Sesamum indicum*, *Musa sapientum*, *Trachyspermum roxburghianum*, *Evolvulus alsinoides* and *Ferula asafoetida*, mixing the aforesaid plant parts in equal proportions to obtain a mixture and optionally adding one or more pharmaceutically acceptable additives/carriers to the above mixture.

In yet another embodiment of the present invention, said process comprises steps of 10 powdering plant parts of *Asparagus racemosus*, *Glycyrrhiza glabra*, *Sesamum indicum*, *Musa sapientum*, *Trachyspermum roxburghianum*, *Evolvulus alsinodes*, *Ferula asafoetida*, *Coriandrum sativum*, *Cyclea peltata* and *Aloe barbadensis*, mixing the aforesaid plant parts in equal proportions to obtain a mixture and optionally adding one or more pharmaceutically acceptable additives/carriers to the above mixture.

In still another embodiment of the present invention, said process comprises the steps of 15 powdering and mixing 5-13 wt. % of plant parts of *Asparagus racemosus*, 5-12 wt. % of plant parts of *Glycyrrhiza glabra*, 8-14 wt. % of plant parts of *Sesamum indicum*, 7-14 wt. % of plant parts of *Musa sapientum*, 4-12 wt. % of plant parts of *Trachyspermum roxburghianum*, 6-12 wt. % of plant parts of *Aloe barbadensis*, 5-12 wt. % of plant parts of 20 *Evolvulus alsinoides*, 6-13 wt. % of plant parts of *Cyclea peltata* 9-14 wt. % of plant parts of *Embelia ribes*, 7-14 wt. % of plant parts of *Coriandrum sativum* and 8-13 wt. % of plant parts of *Ferula asafoetida* to obtain a mixture and optionally adding one or more pharmaceutically acceptable additives/carriers to the above mixture.

In one more embodiment of the present invention, the plant part of *Trachyspermum roxburghianum*, *Embelia ribes* and *Coriandrum sativum* is fruit.

In one another embodiment of the present invention, the plant part of *Cyclea peltata* and *Glycyrrhiza glabra* is root.

In a further embodiment of the present invention, the plant part of *Aloe barbadensis* is elio.

In a furthermore embodiment of the present invention, the plant part of *Asparagus racemosus* is tuber.

In an embodiment of the present invention, the plant part of *Sesamum indicum* is seed.

In another embodiment of the present invention, the plant part of *Musa sapientum* is unripe fruit.

In yet another embodiment of the present invention, the plant part of *Ferula asafoetida* is resin.

In accordance with another object of the present invention, there is provided a method of treating gastric ulcer in a subject, said method comprising administering an effective 5 amount of the synergistic herbal composition essentially comprising of powdered plant parts of *Asparagus racemosus*, *Glycyrrhiza glabra*, *Sesamum indicum*, *Musa sapientum* and *Trachyspermum roxburghianum* and optionally, powdered plant parts of *Cyclea peltata*, *Embelia ribes*, *Coriandrum sativum* *Ferula asafoetida*, *Aloe barbadensis* and *Evolvulus alsinoides* along with one or more pharmaceutically acceptable 10 additives/carriers.

In an embodiment of the present invention, said method comprises administering an effective amount of the synergistic herbal composition comprising of powdered plant parts of *Asparagus racemosus*, *Glycyrrhiza glabra*, *Sesamum indicum*, *Musa sapientum* and *Trachyspermum roxburghianum* in equal proportions, optionally along with one or more 15 pharmaceutically acceptable additives/carriers.

In another embodiment of the present invention, said method comprises administering an effective amount of the synergistic herbal composition comprising of powdered plant parts of *Asparagus racemosus*, *Glycyrrhiza glabra*, *Sesamum indicum*, *Musa sapientum*, *Trachyspermum roxburghianum*, *Evolvulus alsinoides* and *Ferula asafoetida* in equal 20 proportions, optionally along with one or more pharmaceutically acceptable additives/carriers.

In yet another embodiment of the present invention, said method comprises administering an effective amount of the synergistic herbal composition comprising of powdered plant parts of *Asparagus racemosus*, *Glycyrrhiza glabra*, *Sesamum indicum*, *Musa sapientum*, 25 *Trachyspermum roxburghianum*, *Evolvulus alsinodes*, *Ferula asafoetida*, *Coriandrum sativum*, *Cyclea peltata* and *Aloe barbadensis* in equal proportions, optionally along with one or more pharmaceutically acceptable additives/carriers.

In still another embodiment of the present invention, said method comprises administering an effective amount of the synergistic herbal composition comprising 5-13 wt. % of 30 powdered plant parts of *Asparagus racemosus*, 5-12 wt. % of powdered plant parts of *Glycyrrhiza glabra*, 8-14 wt. % of powdered plant parts of *Sesamum indicum*, 7-14 wt. % of powdered plant parts of *Musa sapientum*, 4-12 wt. % of powdered plant parts of *Trachyspermum roxburghianum*, 6-12 wt. % of powdered plant parts of *Aloe barbadensis*,

5-12 wt. % of powdered plant parts of *Evolvulus alsinoides*, 6-13 wt. % of powdered plant parts of *Cyclea peltata* 9-14 wt. % of powdered plant parts of *Embelia ribes*, 7-14 wt. % of powdered plant parts of *Coriandrum sativum* and 8-13 wt. % of plant parts of *Ferula ussafotida* in equal proportions, optionally along with one or more pharmaceutically acceptable additives/carriers.

In one more embodiment of the present invention, the subject is a mammal including human.

In one another embodiment of the present invention, the effective dosage of the composition per day is in the range of 5 to 15g.

10 In a further embodiment of the present invention, the composition can be in the form of tablets, capsules, syrup and any other conventional forms.

In a furthermore embodiment of the present invention, the composition is administered orally, intra-muscularly, and by any other conventional methods.

15 In an embodiment of the present invention, the composition may be used for therapeutic as well as prophylactic treatment of gastric ulcer.

In another embodiment of the present invention, the subject may be administered a bolus dose or a multiple dose.

In yet another embodiment of the present invention, wherein the composition HF2 showed more than 62% protection against cold restraint ulcer model.

20 In still another embodiment of the present invention, wherein the composition HF2 showed more than 30 % protection against aspirin induced ulcer model.

In one more embodiment of the present invention, wherein the composition HF2 reduced the length of hemorrhagic bands to 22.67 ± 4.69 (mm \pm SE) against alcohol induced gastric ulcer.

25 In one another embodiment of the present invention, wherein the composition HF2 has protection index greater than 80 against pyloric ligation induced ulcer.

Brief Description of the Tables

In the tables accompanying the specification,

Table 1 represents the effect of the herbal composition HF2 prepared in accordance with 30 one of the embodiments of the present invention and a standard drug "Omeprazole" against Cold Restraint (at 4° C temp, for 2 hrs.) induced Ulcer (CRU).

Table 2 represents the effect of the herbal composition HF2 prepared in accordance with

one of the embodiments of the present invention and the standard drug "Omeprazole" against aspirin induced gastric ulcer.

Table 3 represents the effect of the herbal composition HF2 prepared in accordance with one of the embodiments of the present invention and the standard drug "Omeprazole" 5 against alcohol induced gastric ulcer in rats.

Table 4 represents the effect of the herbal composition HF2 prepared in accordance with one of the embodiments of the present invention and the standard drug "Omeprazole" against Histamine induced ulcer model.

Table 5 represents the effect of the herbal composition HF2 prepared in accordance with 10 one of the embodiments of the present invention and a standard drug "Omeprazole" against Pyrolic ligation induced ulcer model.

Table 6 gives the composition of the Herbal composition HF2 prepared in accordance with one of the embodiments of the present invention.

Table 7 provides the antigastric ulcer activity of herbal compositions HF3, HF4 and HF5 15 prepared in accordance with the embodiments of the present invention against cold restrained ulcer model, pyloric ligation ulcer model and alcohol induced ulcer model.

Table 8 provides the results of the study conducted to evaluate the synergistic effect of the composition HF2.

Table 9 gives the composition of the Herbal compositions HF3, HF4 and HF5.

20 The invention is further described with respect to the following experiments which are given by way of illustration and therefore should not be construed to limit the scope of the invention in any manner.

Experimental protocol:

Invivo experiments:

25 The Applicants have carried out several experiments under different induced ulcer conditions and the effect of the herbal composition were studied and are tabulated herebelow. The effect of the herbal composition has been compared with respect to a known anti-ulcer drug "Omeprazole".

EXPERIMENT 1: EFFECT ON COLD RESTRAINT ULCERS (CRU) MODEL

METHOD: Adult rats of either sex, weighing 150-175 Gms were fasted for 24 hours with free 30 access to water. The test drugs were administered 45 minutes before immobilizing the animals. The rats were immobilized in the restraint cage at 4°C in BOD incubator for 2 hrs and were sacrificed immediately after the restraint period. (According to the method of Senay and Levine 1967). The abdomen was cut opened; stomach was taken out and incised along the greater curvature to observe the gastric lesions with the help of Magnascope (5X magnification).

The following arbitrary scoring system was used to grade the severity and intensity of the lesions.

1. Shedding of epithelium = 10
2. Petechial and frank hemorrhages = 20
3. One or two ulcers = 30
4. More than two ulcers = 40
5. Perforated ulcers = 50

The presence of any of these lesions was considered as a positive ulcerogenic response which has been shown as percentage of rats showing gastric lesions.

10 The severity of ulcers is expressed in terms of ulcer index, which is the mean score of gastric lesions of all the rats in a group which is defined as:

$$\text{Ulcer Index (U.I.)} = \text{Us} + \text{Up} \times 10^{-1}$$

Where Us = Mean severity of ulcer score and Up - Percentage of animals with Ulcer incidences

15 The percentage protection is calculated as follows:

$$\text{Percentage protection} = (\text{C}-\text{T}/\text{C}) \times 100.$$

Wherein

C = Number of animals showing ulcer response in control group and

T = Number of animals showing ulcer response in test group.

20 The effect of the Herbal Composition of the present invention hereafter referred to as "HF2" against Cold Restraint Ulcer Model (CRU) is given in Table 1. The effect of the standard drug "Omeprazole" is also given in Table 1.

TABLE 1: THE EFFECT OF THE HERBAL COMPOSITION "HF2" AND THE STANDARD DRUG "OMEPRAZOLE" AGAINST COLD RESTRAINT ULCER MODEL (CRU).

Compounds and Doses	Ulcer severity (type of lesions) Scores (No. of rats showing lesions / No. of rats tested)					Mean severity of ulcer score	Percentage of ulcer incidence (No. of rats showing ulcer/total No. of rats used)	Ulcer index	Protection index
	10	20	30	40	50				
Control CRU	-	6/10	4/10	-	-	24	100 (10/10)	12.4	00
CRU+ HF2 (50mg/Kg p.o.)	2/10	2/10	-	-	-	06	40 (4/10)	4.6	62.90
CRU+ Omeprazole (10 mg/Kg p.o.)	3/10	2/10	-	-	-	07	50 (5/10)	5.7	54.03

INFERENCE: Omeprazole showed 54.03 % protection whereas the composition HF2 showed 62.90%, protection against gastric ulcer. Thus it is clear that the composition HF2 provides significantly better protection against cold restraint ulcer model as compared to Omeprazole.

5 **EXPERIMENT 2: EFFECT ON ASPIRIN INDUCED GASTRIC ULCER MODEL**

METHOD: Gastric ulceration was induced by aspirin according to the method of Djahanguiri (1969). Aspirin (150 mg/Kg.) was administered per orally as a suspension in gum-acacia and the animal was sacrificed 5 hr. after the aspirin treatment and the ulcer index with protection index were calculated. The results of the experiment is tabulated in Table 2.

10 The effect of the herbal composition HF2 and the standard drug "Omeprazole" against aspirin induced gastric ulcer is given in Table 2.

TABLE 2: THE EFFECT OF THE HERBAL COMPOSITION "HF2" AND THE STANDARD DRUG "OMEPRAZOLE" AGAINST ASPIRIN INDUCED GASTRIC ULCER

Compounds and Doses	<u>Ulcer severity</u> (type of lesions) <u>Scores</u> (No. of rats showing lesions / No. of rats tested)					Mean severity of ulcer score	Percentage of ulcer incidence (No. of rats showing ulcer/total No. of rats used)	Ulcer index	Protection index
	10	20	30	40	50				
Control Aspirin (150 mg/Kg, p.o.)	-	2/6	4/6	-	-	26.6	100 (6/6)	12.66	00
Aspirin + HF 2 (100 mg/Kg, p.o.)	2/6	2/6	-	-	-	10.0	66.7(4/6)	7.67	39.41
Aspirin + Omeprazole (10 mg/Kg, p.o.)	2/6	2/6	-	-	-	10.0	66.7(4/6)	7.67	39.41

15 **INFERENCE:** Both Omeprazole and the composition HF2 showed equal protection (39.41% protection) against aspirin induced ulcer model.

EXPERIMENT 3: EFFECT ON ALCOHOL INDUCED GASTRIC ULCERS IN RATS

METHOD: Adult rats of either sex were taken; weighing 150 - 175 grams were fasted for 24 hours with free access to water. The test drugs were administered (p.o.) 45 minutes before alcohol administration. 1 ml of chilled absolute alcohol was administered (p.o.) to the rats (According to

Wittetal)³. Immediately after 1 hour, the animals were anesthetized, abdomen was cut opened stomach was taken out and incised along the greater curvature to observe the gastric lesions. The ulcers are examined under the 5X magnification with the help of magnascope. Absolute ethanol lesions appears as blackish lesions grouped in patches of varying size, usually parallel to the major axis of the stomach. The lengths of the lesions are measured and summated to give a total lesion score, then calculated and expressed in percentage.

5 The effect of the herbal composition "HF2" and the standard drug "Omeprazole" against alcohol induced gastric ulcer in rats is given in Table 3.

10 **TABLE 3: THE EFFECT OF THE HERBAL COMPOSITION "HF2" AND THE STANDARD DRUG "OMEPRAZOLE" AGAINST ALCOHOL INDUCED GASTRIC ULCER IN RATS**

Compound	Length of hemorrhagic bands (mm ± SE)
Ethanol control	73.5 ± 1.5
HF 2 (100 mg/kg, p.o.) + Ethanol	22.67 ± 4.69
Omeprazole (100 mg/kg, p.o.) + Ethanol	56.0 ± 9.12

15 **INFERENCE:** The composition of the present invention showed significant protection against this model also. The protection provided by the composition of the present invention is better than Omeprazole.

EXPERIMENT 4: EFFECT ON HISTAMINE INDUCED ULCER MODEL

METHOD: Animals were fasted for 24 hours with access to water. The drug was given orally 1 hour prior to the histamine administration. Histamine was administered in a dose of 0.25 mg/Kg, i.m. at 30 minutes interval -for 7 times and it induced 100 % duodenal ulceration in guinea pig (According to the method of Watt and Eagleton 1964)⁴. The animals were sacrificed after half an hour of last injection under ether anesthesia. The stomach along with duodenum was removed washed thoroughly and examined for the lesions and ulcer index with protection index was calculated. The results of the experiment are tabulated in Table 4.

25 The effect of the herbal composition "HF2" and the standard drug "Omeprazole" against Histamine induced ulcer model is given in Table 4.

TABLE 4: THE EFFECT OF THE HERBAL COMPOSITION "HF2" AND THE STANDARD DRUG "OMEPRAZOLE" AGAINST HISTAMINE INDUCED ULCER MODEL.

Groups and compounds	doses	of	<u>Ulcer severity (type of lesions)</u>					Mean severity of ulcer score	Percentage ulcer incidence (No. of animals showing ulcer/total No. of animals used)	Ulcer index	% Protection	Volume of gastric fluid (mL)
			10	20	30	40	50					
Ulcer Control Histamine (0.25mg/Kg,i.m.)x7	—	—	1/3	2/3	—	36.6	100 (3/3)	13.66	00		4.33 ± 1.01	
Histamine + HF2 (50 mg/Kg, p.o.)	—	—	1/3	—	—	10.0	33.3(1/3)	4.33	68.3		1.60 ± 0.7	
Histamine + Omeprazole (10 mg/kg, p.o.)	—	1/3	—	—	—	6.66	33.3 (1/3)	3.99	70.79		1.0 ± 0.2	

INFERENCE: In this model, Omeprazole showed 70.79% protection whereas the composition HF2 showed 68.3% protection. In comparison, the composition HF2 provides more or less equal protection.

EXPERIMENT 5: EFFECT ON PYLORIC LIGATION INDUCED ULCER MODEL

METHOD: Animals were fasted for 24 hours in the raised mesh bottom cages to prevent coprophagia and were allowed free access to water. The control group of rats was feed with the vehicle and the experimental groups with their respective drugs 45 minutes prior to the ligation. The animal was anesthetized, abdomen was cut opened under xiphoid process, and the pyloric portion of

the stomach was slightly lifted and ligated avoiding any damage to the adjacent blood vessels (According to the method of Shay et al. 1945). The animals were stitched and kept for 4 hours with free access to water. After 4 hours the animals were sacrificed under ether anesthesia and the stomach was dissected out incised along the greater curvature. The stomach was washed thoroughly and the ulcer index was scored as per in other ulcer models. The results of the experiment are tabulated in Table 5.

The effect of the herbal composition "HF2" and the standard drug "Omeprazole" against Pyloric ligation induced ulcer model is given in Table 5.

TABLE 5: EFFECT OF OMEPRAZOLE AND THE HERBAL COMPOSITION HF2 AGAINST PYLORIC LIGATION INDUCED ULCER

Groups	Ulcer Index	Protection Index
Ligation Control	16.6	0.0
Ligation + HF2	1.65	84.08
Ligation + Omeprazole (10mg/Kg,p.o.)	6.6	51.44

INFERENCE: The composition of the present invention showed better protection than Omeprazole in the pyloric ligation induced ulcer model.

EXPERIMENT 6: EFFECT OF THE PRESENT COMPOSITION ON ACETYLCHOLINE AND HISTAMINE INDUCED CONTRACTION OF GUINEA-PIG ILEUM

METHOD: A piece of 2 - 3 cm of the terminal ileum of a freshly killed Guinea pig was suspended in an organ bath containing Tyrode solution at 34° C and bubbled with fresh air. Contraction was induced by submaximal contraction of acetylcholine chloride (1 [ig/mL] and Histamine (1 ng/mL) and it was recorded on a kymograph (According to the method of Patnaik 1992).

The composition HF2 (up to 250 ng / mL) did not exert any significant influence on isolated tissue preparation for anticholinergic (acetylcholine-induced contraction of Guinea-pig ileum) and Fk-anti-histaminic (Histamine induced contraction of Guinea-pig ileum) activity.

EXPERIMENT 7: HERBS AND PREPARATION OF THE COMPOSITION

For the purpose of conducting animal experiment all the herbs are washed dried and pulverised. All the herbs are taken in the proportion as shown in Table 6. The whole mixture is blended well and used for administering.

The components and their proportions of the standard herbal composition according to one embodiment of the present invention are listed in Table 6. The part of the herb which is used is also mentioned. The placebo preparation is designed to taste, smell and look like an Ayurvedic herbal composition.

TABLE 6: THE COMPOSITION OF THE HERBAL COMPOSITION HF2

S. No.	Name of the plant and its part used	Percentage
1.	<i>Aloe barbadensis</i> (elio)	6-12%
2.	<i>Asparagus racemosus</i> (Tubers)	5-13%
3.	<i>Glycyrrhiza glabra</i> (roots)	5-12%
4.	<i>Sesamum indicum</i> (seeds)	8-14%
5.	<i>Evolvulus alsinoides</i> (whole plant)	5-12%
6.	<i>Musa sapientum</i> (unripe fruit)	7-14%
7.	<i>Trachyspermum roxburghianum</i> (fruits)	4-12%
8.	<i>Embelia ribes</i> (fruits)	9-14%
9.	<i>Coriandrum sativum</i> (fruits)	7-14%
10.	<i>Cyclea peltata</i> (root)	6-13%
11	<i>Ferula asafoetida</i> (resin)	8-13%

TABLE 7: ANTIGASTRIC ULCER ACTIVITY OF THE HERBAL COMPOSITIONS HF3, HF4 AND HF5

Formulation	Cold restrained ulcer model	Pyloric ligation model	Alcohol induced ulcer model
HF3	66.69	41.75	86.54
HF4	45.86	17.0	79.42
HF5	45.86	62.75	85.75

In order to conduct a study on the synergistic effect, the herbal composition HF2 was taken and each component was removed and the effect of the resultant composition against cold restrained gastric ulcer model was studied. The results of the experiment thus conducted is tabulated in Table 8. It was concluded from the above experiments that the batch prepared by the removal of Emblica ribes has shown very good protection.

TABLE 8: RESULTS OF THE SYNERGISTIC EFFECT STUDY

S. No.	Details of Batch	Ulcer Index
1	HF2 without <i>Aloe barbadensis</i>	26.6
2	HF2 without <i>Asparagus racemosus</i>	11.6
3	HF2 without <i>Glycyrrhiza glabra</i>	15.0
4	HF2 without <i>Sesamum indicum</i>	20.0
5	HF2 without <i>Evolvulus alsinoides</i>	13.3
6	HF2 without <i>Trachyspermum roxburghianum</i>	20.0
7	HF2 without <i>Embelica ribes</i>	8.3
8	HF2 without <i>Coriandrum sativum</i>	10.0
9	HF2 without <i>Cyclea peltata</i>	11.66
10	HF2 without <i>Ferula asafetida</i>	13.0
11	HF2 without <i>Musa sapientum</i>	20.0

TABLE 9: COMPOSITION OF THE HERBAL COMPOSITIONS HF3, HF4 AND HF5

HF3	HF4	HF5
1. <i>Asparagus racemosus</i> 2. <i>Glycyrrhiza glabra</i> 3. <i>Sesamum indicum</i> 4. <i>Musa sapientum</i> and 5. <i>Trachyspermum roxburghianum</i> All in equal proportions	1. <i>Asparagus racemosus</i> 2. <i>Glycyrrhiza glabra</i> 3. <i>Sesamum indicum</i> 4. <i>Musa sapientum</i> 5. <i>Trachyspermum roxburghianum</i> 6. <i>Evolvulus alsinoides</i> and 7. <i>Ferula asafoetida</i> All in equal proportions	1. <i>Asparagus racemosus</i> 2. <i>Glycyrrhiza glabra</i> 3. <i>Sesamum indicum</i> 4. <i>Musa sapientum</i> 5. <i>Trachyspermum roxburghianum</i> 6. <i>Evolvulus alsinoides</i> 7. <i>Ferula asafoetida</i> 8. <i>Coriandrum sativum</i> 9. <i>Cyclea peltata</i> and 10. <i>Aloe barbadensis</i> All in equal proportions